Remodeling Epithelial Cell Organization: Transitions Between Front–Rear and Apical–Basal Polarity

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Polarized epithelial cells have a distinctive apical–basal axis of polarity for vectorial transport of ions and solutes across the epithelium. In contrast, migratory mesenchymal cells have a front–rear axis of polarity. During development, mesenchymal cells convert to epithelia by coalescing into aggregates that undergo epithelial differentiation. Signaling networks and protein complexes comprising Rho family GTPases, polarity complexes (Crumbs, PAR, and Scribble), and their downstream effectors, including the cytoskeleton and the endocytic and exocytic vesicle trafficking pathways, together regulate the distributions of plasma membrane and cytoskeletal proteins between front–rear and apical–basal polarity. The challenge is to understand how these regulators and effectors are adapted to regulate symmetry breaking processes that generate cell polarities that are specialized for different cellular activities and functions.

THE BASIC DESIGN OF POLARIZED EPITHELIAL CELLS

Epithelial cells are distinguished from other cell types by their organization into adherent groups of cells that partition the organism into discrete compartments—generally, a specialized internal compartment separated and protected from the external environment by the epithelium. This organization provides a number of unique physiological properties. Most importantly, a closed epithelium enables the regulated exchange of nutrients and waste between the internal and external environments (Fig. 1A) (reviewed in Cereijido et al. 2004).

This conserved function of polarized epithelial cells requires that membrane proteins are sorted and retained in the correct apical or basolateral membrane domain (Fig. 1B). A major sorting site for newly synthesized plasma-membrane proteins is the trans-Golgi complex (TGN) (the exocytic pathway) (reviewed in Folsch 2008; Mellman and Nelson 2008), but additional sorting events between the TGN and plasma membrane domains (Gravotta et al. 2007) and different membrane domains (transcytosis) (Casanova et al. 1990) occur in the endocytic pathway (Fig. 1B). Some vesicle trafficking between the TGN and the plasma

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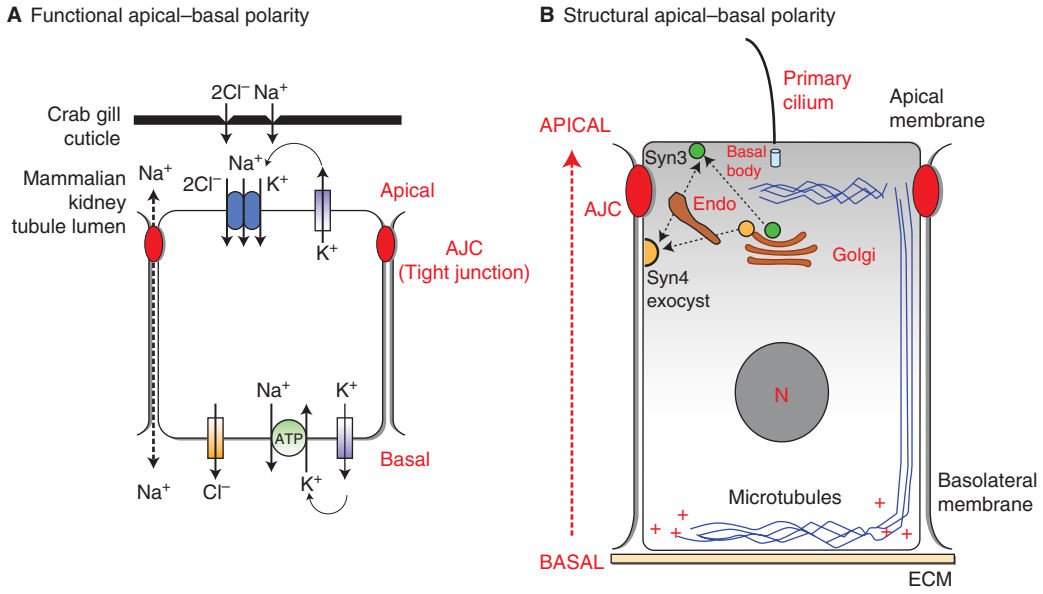

Figure 1. Functional and structural organization of polarized epithelia. (*A*) Functional apical–basal polarity. Physiological studies of transporting epithelia across the phyla (e.g., crab gill and mammalian kidney nephron) has revealed a remarkable conservation in the distribution of ion channels (Cl channel, K channel) transporters (Na,K,2Cl transporter) and pumps (Na/K-ATPase) between the apical and basolateral plasma membrane domains. The polarized distribution of these proteins generates an apical–basal sodium gradient that is used to move other ions and solutes across the epithelium. (Redrawn and adapted from Cereijido et al. 2004.) (*B*) Structural apical–basal polarity. Polarized epithelial cells have a distinctive apical–basal polarity in the orientation of cell–cell and cell–extracellular matrix (ECM). Major structures of these cells are also organized in the apical–basal axis: The organization of plasma membrane domains (apical and basolateral), junctional complexes (APC, apical junctional complex), the centrosome (basal body), microtubules and primary cilium, and the secretory pathway (Golgi). For details, see text.

membrane occurs along microtubules (Jaulin et al. 2007; Lafont et al. 1994), which, compared with migratory cells (see Fig. 2A), have an unusual organization in polarized epithelial cells (Bacallao et al. 1989) (Fig. 1B). Finally, the docking and fusion of vesicles with the correct membrane domain requires specific vesicle tethering (exocyst) and SNARE complexes (Fig. 1B) (reviewed in Mellman and Nelson 2008).

Several mechanisms maintain the distributions of proteins to the apical or basolateral membrane domain. First, the tight junction acts as a molecular fence at the boundary between the apical and basolateral membrane domains (apical junctional complex [AJC]) (Fig. 1B) to prevent the free diffusion of proteins from one domain to the other, and a gate to the paracellular diffusion of ions and solutes (Fig. 1A) (reviewed in Shin et al. 2006). Second, several classes of membrane proteins bind to a cytoplasmic scaffold complex of ankyrin–spectrin on the basolateral membrane, including ion transporters and channels (reviewed in Bennett and Healy 2008). These interactions are important in regulating membrane protein trafficking, and retention in different membrane domains (reviewed in Bennett and Healy 2008).

Evolution and Developmental Origins of Polarized Epithelia

Epithelia arose at the time of the emergence of primitive metazoans in Precambrian times, approximately 600 million years ago. The evolution of mesenchymal cells in bilaterians enabled a further diversification in the

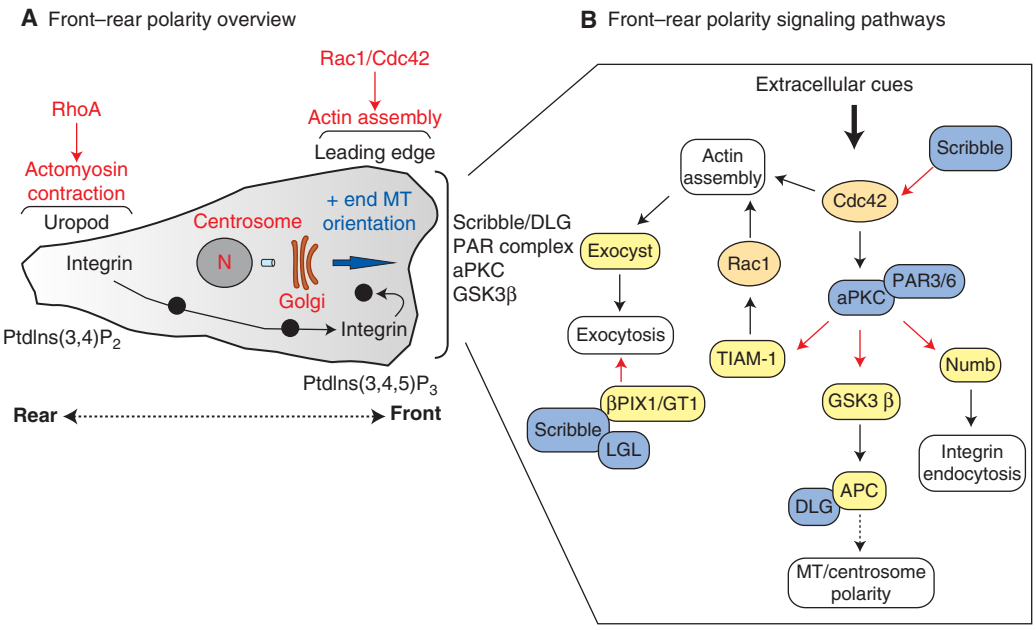

Figure 2. Functional and structural organization of migratory mesenchymal cells. (*A*) Front–rear polarity overview. Migratory cells have a distinctive organization between the front of the cell (leading edge) and rear (uropod). Rho family GTPase activities have different functions in inducing actin polymerization at the leading edge (Cdc42, Rac1), and actomyosin contraction at the rear (RhoA). The centrosome, microtubules, and the secretory pathway (Golgi) are oriented toward the front of the cell. Endocytic and exocytic pathways are also oriented in the rear–front orientation, which allows internalization of integrins from the rear, and exocytosis and endocytosis of integrins in the front, all of which are required for cell migration. Phosphatidylinositides have a polarized distribution in the front–rear polarity. Polarity protein complexes are localized to the front of the cell (Scribble/DLG and PAR/aPKC). (*B*) Front–rear polarity signaling pathways. Polarity protein complexes (blue) are upstream and downstream of Rho small GTPases (Rac1 and Cdc42) and their downstream effectors (yellow) and end-point effects (white). For details, see text.

distribution and organization of epithelial structures (Baum et al. 2008). Unlike epithelial cells, mesenchymal cells show weak cell–cell adhesion and are motile, allowing them to migrate to different sites in the body cavity where they convert to epithelial cells and contribute to the formation of secondary epithelia. This provided additional complexity in compartmentalization in metazoans that lead to the formation of physiologically different tissues and organs (Magie and Martindale 2008).

The process of formation of polarized epithelia during development is initiated by the coalescence of migratory (mesenchymal and epithelial) cells into cell aggregates that undergo epithelial differentiation. The cellular transformation from migratory cells with a front–rear polarity designed for directional migration, to an epithelium with an apical–basal polarity designed for vectorial ion and solute transport is complex. Signaling pathways that initiate this mesenchymal-to-epithelial transition (MET) involve soluble growth factors and their receptors, and downstream signaling pathways (Baum et al. 2008; Dressler 2006), and changes in patterns of gene expression (Boyle and de Caestecker 2006; van der Flier and Clevers 2008). However, remodeling from front–rear to apical–basal polarity also involves the reorganization of generic structures and cellular processes common to all cell types, including the cytoskeleton, endocytic and exocytic vesicle trafficking pathways, and mechanisms for localizing and retaining

membrane proteins to different plasma membrane domains. Here, I focus on master regulators and signaling pathways that control front–rear polarity of migratory mesenchymal cells, establishing the basic design of the developmental precursors to epithelia. I then discuss how pathways and regulators common to both mesenchymal and epithelial cells are reused and adapted to regulate the symmetry breaking processes that lead to the conversion between front–rear and apical–basal polarity.

FRONT–REAR POLARITY IN MIGRATORY CELLS

Migratory mesenchymal cells show front–rear polarity required for persistent, directional cell migration (Fig. 2A) (reviewed in Ridley et al. 2003). Many different external cues initiate front–rear polarity, including growth factors and the extracellular matrix. Conversion of those cues into directional migration requires global changes in cell organization by protein complexes and signaling pathways that control the cytoskeleton and protein trafficking.

Front–Rear Polarity of Phosphatidylinositides

A central feature of polarized migrating cells, best studied in neutrophils and *Dictyostelium*, is the front–rear polarity of different phosphatidylinositides in the plasma membrane (Funamoto et al. 2002; Iijima and Devreotes 2002; Wang et al. 2002). Generally, phosphatidylinositide-3,4,5-triphosphate (PtdIns $(3,4,5)P_3$) is enriched in the plasma membrane at the front of the cell, whereas phosphatidylinositide-3,4-bisphosphate (PtdIns $(3,4)P_2$) is enriched everywhere else, including the rear (Fig. 2A). The different distributions of phosphatidylinositides was thought to be a consequence of the spatial activation of phosphoinositide 3-kinase (PI3-kinase) at the front of the cell, and phosphatase and tensin homolog (PTEN) elsewhere. Although this picture has become more complex (Stephens et al. 2008), the front–rear distribution of PtdIns$(3,4,5)P_3$ and PtdIns$(3,4)P_2$ are important in generating asymmetry in the activation of intracellular pathways required for membrane protrusions in axonal growth cones (Arimura and Kaibuchi 2005), migrating neutrophils (Stephens et al. 2008), and other cells (Ridley et al. 2003).

Front–Rear Polarity of Rho GTPases

The generation of front–rear polarity is mediated by the localized activation of members of the Rho family of small GTPases (Li et al. 2008; reviewed in Iden and Collard 2008). In general, Cdc42 and Rac1 are activated at the front of the cell, which results in the rapid and dynamic assembly of actin filaments mediated by the Arp2/3 complex and formins (Pollard 2007), and the capture (stabilization) and polarized orientation of microtubules by mDia (Palazzo et al. 2001) and microtubule plus-end binding proteins (Akhmanova et al. 2001; Wen et al. 2004) (reviewed in Li et al. 2008) (Fig. 2A). These localized changes in the actin and microtubule cytoskeletons generate membrane protrusions, dynamic assembly and disassembly of integrin-based contacts with the extracellular matrix, and forward movement of the leading edge (Li et al. 2008; Ridley et al. 2003). RhoA, on the other hand, is activated at the rear of the cell and promotes the assembly and activation of contractile actomyosin networks that are necessary for detachment of the rear of the cell from the extracellular matrix (Fig. 2A) (Ridley et al. 2003). Local activation of these small GTPases affects cell organization globally by maintaining localized sites of actin polymerization (front) and contractions (rear). Inhibition of local Rac1/Cdc42 or RhoA activity, or disruption of the polarized organization of the actin and microtubule cytoskeletons results in a global loss of directional migration by neutrophils (Xu et al. 2003).

Roles of Polarity Complexes in Front–Rear Functions of Rho GTPase and Cytoskeleton

Polarity complexes regulate the cytoskeleton either upstream or downstream of Rho family GTPases (Fig. 2B) (reviewed in Iden and

Collard 2008). Polarity proteins were originally identified in epithelia as protein complexes involved in regulating apical–basal polarity, but they are also found in migrating mesenchymal cells. They include three protein complexes, each defined by its core interacting proteins: the Scribble complex (Scribble, DLG, and LGL), the PARtition (PAR) complex (PAR3/PAR6/atypical protein kinase C [aPKC]) and PAR4/LKB1, and the Crumbs complex (Crumbs, PALS1, and PATJ) (see Fig. 2B) (see McCaffrey and Macara 2009; Prehoda 2009). These proteins are generally classified as tumor suppressors (reviewed in Bilder 2004), but how they control cell proliferation is poorly understood (see the end of the article for further discussion). Nevertheless, it is clear that they play essential roles in cell organization. They are generally localized at the front of migrating cells (Fig. 2B), although Scribble and DLG have also been found at the rear of migrating T cells (Ludford-Menting et al. 2005). Little is known about plasma membrane binding sites for Scribble, or other Polarity complexes at the front (or rear) of cells.

Several mechanisms involving Polarity complexes locally activate Cdc42 and Rac1 at the leading edge plasma membrane (Fig. 2B). Scribble, in a complex with βPIX (PAK-interacting exchange factor)—a guanine exchange factor for Cdc42/Rac1—and GIT1 (G-protein coupled receptor interacting protein 1) (Audebert et al. 2004), controls Cdc42 activation and localization (Osmani et al. 2006). Knockdown of Scribble levels in mammalian tissue culture cells also causes a decrease in activation of Rac1, indicating that the Scribble complex regulates Rac1 activity directly or indirectly (Zhan et al. 2008). Additional mechanisms regulate Cdc42 and Rac1 activation at the leading edge (reviewed in Arimura and Kaibuchi 2005), including integrin engagement with the extracellular matrix (Etienne-Manneville and Hall 2001), Rap1, another Ras family GTPase (Bos 2005), which activates integrins and Cdc42 (Takahashi et al. 2008), and Rac1 (Gerard et al. 2007) at the front of migrating cells. Several feedback loops may be involved in maintaining active Cdc42 at the front, including PI3-kinase, which concentrates PtdIns(3,4,5)P_3 at the front (Raftopoulou and Hall 2004), and PAR4/LKB1 (Zhang et al. 2008). Interestingly, ectopic expression of PAR4/LKB1 in single epithelial cells results in a dramatic global polarization of the cytoskeleton and the formation of distinct plasma membrane domains in the absence of either cell–cell or cell–extracellular matrix adhesion (Baas et al. 2004). Thus, at least in the context of ectopic expression, PAR4/LKB1 appears to be an example of a regulator of autonomous symmetry breaking. PAR4/LKB1 substrates include another serine/threonine kinase PAR1 and the family of ELKL-motif kinases (EMKs), also known as microtubule-affinity-regulating kinases (MARKs) (Illenberger et al. 1996). A variety of studies in fibroblasts, epithelial cells, and *Drosophila* indicate that PAR1 and MARKs regulate microtubule remodeling and organization, and the delivery of transport vesicles to the plasma membrane (Cohen et al. 2004a; Cohen et al. 2004b; Elbert et al. 2005).

aPKC, a component of the PAR3/PAR6 Polarity complex, is a downstream effector of activated Cdc42 (Fig. 2B), although it may be localized to the front of the cell independently of Cdc42 by PATJ (Shin et al. 2007), a component of the Crumbs Polarity complex. aPKC has a number of substrates critical for the polarization of migrating cells (Fig. 2B). One substrate is T-cell-lymphoma invasion and metastasis1 (TIAM1) (Nishimura et al. 2005), a GEF that activates Rac1 (Pegtel et al. 2007). Another substrate is glycogen synthase kinase-3β (GSK3β). GSK3β is inactivated upon aPKC phosphorylation, one result of which is that nonphosphorylated APC, normally a target of active GSK3β, binds to and stabilizes microtubules at the plasma membrane (Zumbrunn et al. 2001). Interestingly, DLG, a component of the Scribble Polarity complex, binds APC, thereby localizing DLG to the front of migrating cells (Etienne-Manneville et al. 2005) (Fig. 2B). Finally, orientation of microtubules in the front–rear axis affects the orientation of the centrosome, also called the microtubule organization center (Fig. 2A),

which is critical for maintaining overall cell polarity and directional migration (Etienne-Manneville and Hall 2003).

Front–Rear Polarization of Endocytic and Exocytic Membrane Trafficking Pathways

Membrane protein distributions in migratory cells are organized in the front–rear orientation by the exocytic and endocytic pathways (Fig. 2A). Local exocytosis of proteins occurs at the front of migrations cells (for discussion, see Bretscher 2008). It is unclear, however, if newly synthesized proteins are also targeted specifically to the front of migrating cells. Although specific sorting of membrane proteins in the exocytic pathway to apical and basolateral membrane domains is generally thought to be a specialization of epithelial cells polarized in the apical–basal axis (Fig. 1B), fibroblastic cells appear to have a similar capacity (Yoshimori et al. 1996). Further studies are required, however, to determine whether protein sorting in the TGN and separate delivery of different classes of proteins to different membrane domains is important for establishing or maintaining front–rear polarity in response to an extracellular cue.

The redistribution of membrane proteins after delivery to the plasma membrane occurs via the endocytic pathway. Integrins are an important class of proteins that are redistributed from the rear to the front of the cell by the endocytic pathway (Hopkins et al. 1994; Lawson and Maxfield 1995) (Fig. 2A). The endocytic adaptor protein Numb (Salcini et al. 1997), another substrate for aPKC (Nishimura and Kaibuchi 2007), is involved (Fig. 2B). In its nonphosphorylated state, Numb binds to and induces the endocytosis of integrins, and promotes cell migration aPKC phosphorylation of Numb inhibits Numb binding to integrins, and reduces cell migration (Nishimura and Kaibuchi 2007). It is important to recall that aPKC phosphorylation of other substrates also promotes cell migration (see the previous discussion), indicating that control of aPKC activity (or substrate accessibility) or location may fine tune cell polarization and migration.

Several protein complexes that control vesicle delivery to the plasma membrane are localized to the front of migrating cells (Fig. 2B). The complex of Scribble, βPIX, and GIT1 locally regulates Ca^{++}-dependent exocytosis at synapses (Audebert et al. 2004), and the distribution of this complex to the front of the cell (Fig. 2B) could play a similar role to promote local transport and vesicle fusion with the leading edge. Another protein in the Scribble Polarity complex, LGL, may also play a role in vesicle fusion at the plasma membrane. Both mammalian LGL (Musch et al. 2002) and the yeast homolog Sro7/77 (Lehman et al. 1999) bind t-SNAREs, and deletion of Sro7/77 in yeast (Lehman et al. 1999) or LGL in neuronal cells (Klezovitch et al. 2004) results in inhibition of some protein delivery to the plasma membrane.

The Exocyst complex, which is thought to tether transport vesicles to sites of fusion with the plasma membrane (Wu et al. 2008), is also localized to the front of migratory cells (Fig. 2B) (Spiczka and Yeaman 2008; Zuo et al. 2006). The exocyst interacts with a number of proteins that could localize it to the leading edge, including paxillin (a structural and signaling protein associated with integrin focal adhesions), the βPIX-GIT1 complex (Spiczka and Yeaman 2008), and Apr1 (a protein in the Arp2/3 complex) (Zuo et al. 2006). Importantly, knockdown of exocyst proteins results in decreased delivery of integrins to the front of the cell and a decreased rate of cell migration (Spiczka and Yeaman 2008; Zuo et al. 2006), further supporting the role of polarized trafficking of proteins to the front of migratory cells.

In summary, regulation of front–rear polarity in migratory cells requires localized activation of different Rho family small GTPases at the front (Cdc42, Rac1) and rear (Rho) of the cell that results in the polarized orientation and assembly of the actin and microtubule cytoskeletons. Polarity complexes, particularly the Scribble complex and components of the PAR complex, play multiple roles in controlling the local distribution and activation of Rac1 and Cdc42 at the front of

the cell, downstream regulation of cytoskeleton organization and assembly, and local regulation of the endocytic and terminal exocytic machinery that are required for remodeling of membrane protein distributions.

APICAL–BASAL POLARITY IN EPITHELIAL CELLS

The transition from migratory cells to the establishment of a polarized simple epithelium requires the aggregation of cells through specific cell–cell interactions, followed by epithelial differentiation. In general, the adhesive surfaces, formed by interactions between cells and with the extracellular matrix, form the basolateral plasma membrane domain. Characteristically, the apical plasma membrane forms on the "nonadhesive" surface. In a few exceptional cases, however, a nonadhesive surface is present immediately: For example, the open surface of epithelial cell monolayers grown in tissue culture, the outside surface of the preimplantation mammalian embryo, or syncytial blastoderm of *Drosophila*. The formation of an apical surface within cell aggregates is more complex.

The First Overt Evidence of Apical–Basal Polarity—Orientation of the Apical/Luminal Domain

Within an aggregate of cells, a luminal nonadhesive surface is not provided and, therefore, has to be formed de novo. Several mechanisms appear to generate a nonadhesive surface and a lumen within an aggregate of cells (reviewed in Bryant and Mostov 2008): (1) Selective apoptosis of cells in the center of the aggregate (Mailleux et al. 2008) removes cells, leaving behind a luminal space; (2) Insertion of apical proteins from intracellular stores into the cell–cell contact, coupled with exclusion of E-cadherin and other basolateral proteins from that site (Ferrari et al. 2008; Jaffe et al. 2008; Ojakian et al. 1997). In this case, the lack of cell–cell adhesion proteins would allow formation of a nonadhesive, luminal surface on cells containing apical membrane proteins; (3) Vectorial fluid secretion into the luminal space mediated by polarized distributions of ion channels and pumps between the apical (e.g., CFTR) and basolateral membrane (e.g., Na/K-ATPase) (Ferrari et al. 2008; Houghton et al. 2003; Jaffe et al. 2008). Coupled with the loss of cell–cell adhesion on the forming apical membrane (see #2 above), vectorial pumping of fluid would help to fill the luminal space; and (4) Repulsion of E-cadherin cell–cell adhesion (e.g., during formation of the heart tube in the *Drosophila* embryo) (Santiago-Martinez et al. 2008). In this case, inhibition of E-cadherin-mediated cell–cell adhesion by Slit and Robo pathways induces formation of a luminal space.

Cell adhesion to the extracellular matrix (ECM) is critical for signaling the formation of an apical membrane and luminal space (reviewed in Bryant and Mostov 2008). In its simplest role, ECM adhesion enables cells to distinguish an adhesive surface (attached to the ECM) and a nonadhesive surface. For example, single mammary epithelial cells attached to an ECM (i.e., in the absence of cell–cell adhesion) secrete β-casein from the apical surface specifically (Streuli et al. 1995), and RNA envelope viruses, which normally bud from the apical (Influenza virus) and basolateral membrane (Vesicular Stomatitis virus, VSV) of polarized monolayers of MDCK cells, but bud from different sites on the plasma membrane of single MDCK cells attached to a substratum (Rodriguez-Boulan and Pendergast 1980).

The specialized role of the ECM in the de novo formation of the lumen/apical membrane is important within cell aggregates such as three-dimensional MDCK epithelial cysts (reviewed in Bryant and Mostov 2008). Although details of the mechanisms involved are not fully understood, it appears that the initial step is Rac1-dependent adhesion of integrins to the ECM protein laminin (O'Brien et al. 2001) (Fig. 3). Subsequently, the asymmetric distribution of PtdIns(3,4,5)P_3 to the basolateral membrane and PtdIns(3,4)P_2 to the apical membrane initiates the localization of Cdc42 by annexin II (Martin-Belmonte et al. 2007), and the PAR complex to the

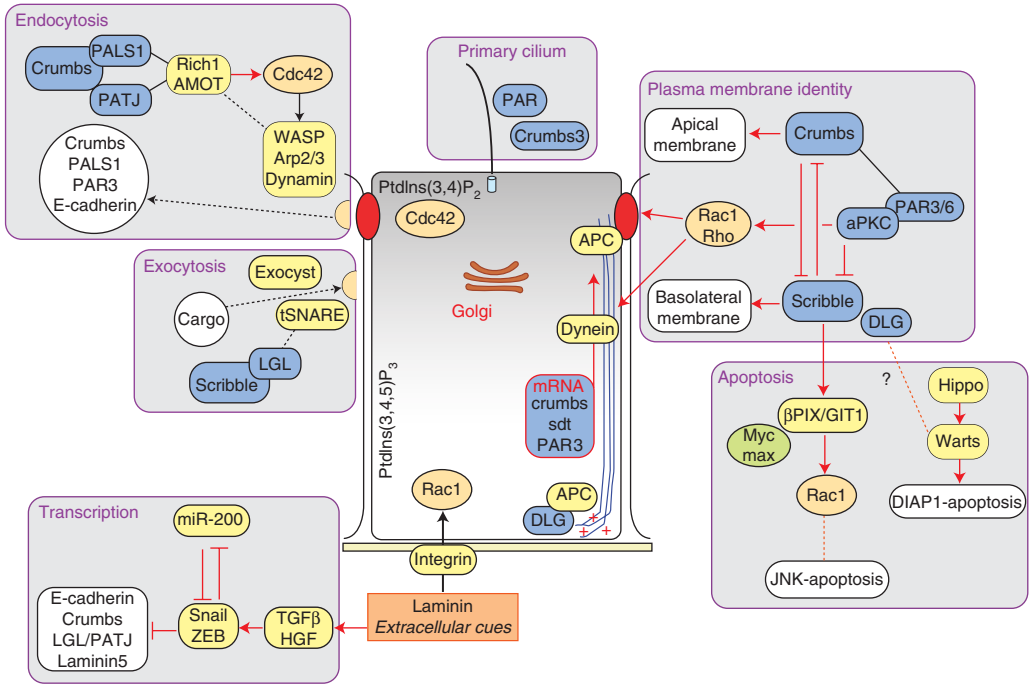

Figure 3. Functional and structural organization of polarized epithelial cells. *Center*: Phosphatidylinositides have a distinctive apical–basal polarity; PtdIns(3,4)P_2 is localized in the apical membrane, and PtdIns(3,4,5)P_3 is localized in the basolateral membrane. Signals from the extracellular matrix (laminin) through integrins and Rac1 activity orient cells, and are required for formation of the apical/luminal domain. Microtubules, which are polarized in the apical–basal axis, are anchored at the basal and lateral membranes (AJC) by APC and other protein complexes; microtubule/dynein-dependent delivery of mRNAs to the apical region is required for proper localization of Crumbs, Sdt (PALS1), and PAR3. *Modules*: Polarity protein complexes regulate several pathways critical for the establishment and maintenance of apical–basal polarity. Generally, expression of E-cadherin, Polarity protein complexes, and ECM proteins are required to establish and maintain apical–basal polarity (epithelial program). Extracellular cues, including growth factors/cytokines (e.g., TGF-β or HGF) and the transcriptional repressors Snail and ZEB1 down-regulate expression of this epithelial program causing the loss of epithelial differentiation and cell–cell adhesion, and resulting in a front–rear polarization and cell migration (the *transcriptional module*). *Plasma membrane module* involves mutually antagonistic regulation of the Crumbs (apical domain) and Scribble (basolateral domain) complexes, and the PAR complex. The Par complex also locally regulates Rac1 and Rho at the AJC (see text for details). Components of the Crumbs (Crumbs3) and PAR complexes are localized to the primary cilium (the *primary cilium module*) and regulate global cell polarity. The Crumbs complex (the *endocytosis module*) and Scribble complex (the *exocytosis module*) control membrane protein organization and stability at the AJC (see text for details). Finally, the Scribble complex appears to play a role in regulating apoptosis (the *apoptosis module*).

apical region of the cell (see the following). It is unclear how PtdIns(3,4,5)P_3 and PtdIns(3,4)P_2 are locally synthesized and localized to different membrane domains. One mechanism may involve localization of PTEN, which converts PtdIns(3,4,5)P_3 to PtdIns(3,4)P_2, to the PAR complex at the AJC (von Stein et al. 2005). This could prevent PtdIns(3,4,5)P_3 accumulation in the apical domain. Localization of these different phosphatidylinositides to the apical and basolateral membranes is important in apical–basal polarity as ectopic addition of either phosphatidylinositide to the "wrong" plasma membrane domain results in reversal of the apical–basal polarity of membrane proteins (Martin-Belmonte et al. 2007).

Apical–Basal Polarization of Endocytic and Exocytic Membrane Trafficking Pathways

As the cell generates apical–basal polarity, the exocytic and endocytic pathways establish a complex interrelationship that regulates correct sorting of newly synthesized proteins to and between the apical and basolateral membrane domains.

A major sorting site for newly synthesized proteins in the exocytic pathway is the TGN (Fig. 1B). Two pathways have been identified that sort apical proteins by clustering them into a microdomain of the TGN from which apical transport vesicles form (reviewed in Schuck and Simons 2004): clustering by glycolipid rafts enriched in sphingolipids and cholesterol (Paladino et al. 2007), or by association with galectin-3 oligomers (Delacour et al. 2005). Sorting in the basolateral pathway involves recognition of diverse cytoplasmic sorting signals by cytosolic factors, which cluster these proteins into a TGN micro-domain separate from that containing apical proteins. Many of these basolateral signals are either tyrosine- or dileucine-based and are recognized by cytosolic adaptor proteins (AP) and clathrin (reviewed in Folsch 2008; Mellman and Nelson 2008). APs and clathrin are also involved in sorting proteins in the endocytic pathway (Edeling et al. 2006), and several studies have showed the intersection of the basolateral exocytic and endocytic pathways in basolateral protein sorting (Gravotta et al. 2007) and transcytosis of proteins between different membrane domains (Casanova et al. 1990).

Some of the vesicle trafficking between the TGN and plasma membrane, and transcytosis between membrane domains occurs along microtubules (Jaulin et al. 2007; Lafont et al. 1994). Microtubules are organized into bundles aligned in the apical–basal axis of the cell, with plus ends at the basal membrane and minus ends in the apical cytoplasm (Fig. 1B) (Bacallao et al. 1989). How microtubules are maintained in this apical–basal organization is poorly understood. Adenomatous polyposis coli (APC), a microtubule binding protein associated with the plasma membrane, forms a template for binding the basal network of microtubules (Reilein and Nelson 2005), and is associated with microtubules and the adherens junction in some cell types (Hamada and Bienz 2002) (Fig. 3). Microtubules may also attach indirectly to the cadherin–catenin complex (adherens junction) through interactions with the dynactin complex (Lien et al. 2008; Ligon and Holzbaur 2007), and p120catenin and kinesin 1 (Chen et al. 2003). A population of microtubules is also localized to the adherens junction through their minus ends by Nezha and PLEKHA7 that bind to the cadherin–catenin complex (Meng et al. 2008).

Docking and fusion of vesicles with the correct membrane domain requires specific vesicle tethering and SNARE complexes (Fig. 1B). The exocyst vesicle-tethering complex is localized to the apex of the lateral membrane domain and specifies basolateral vesicle delivery there (Grindstaff et al. 1998). However, the role of the exocyst in vesicle trafficking in apical–basal polarized cells may be more multifaceted. The exocyst has also been localized to apical endosomes where it regulates transcytosis of membrane proteins between the basolateral and apical membranes (Oztan et al. 2007), and at the apically localized primary cilium (Overgaard et al. 2009). In both cases, the exocyst likely acts as a vesicle-tethering complex, similar to its function at the plasma membrane.

Different t-SNAREs are localized to the apical (syntaxin 3) and basolateral (syntaxin 4) membranes (Low et al. 1996) (Fig. 3) and specify the delivery of cognate transport vesicles with the correct membrane domain. This differential localization is required for correct vesicle delivery as mislocalization of syntaxin 3 to the basolateral membrane causes apical proteins to be mistargeted to the basolateral membrane (Sharma et al. 2006).

Apical–Basal Organization and Function of Polarity Proteins

A distinctive feature of polarized epithelia is the spatial distribution of intercellular junctional complexes and Polarity protein complexes (Crumbs, PAR, and Scribble). In vertebrate and

invertebrate epithelial cells, the adherens junction and the tight junction are localized to the apex of the lateral membrane (the AJC) at the boundary between the apical and basolateral plasma membrane domains. In invertebrates, the functional homolog of the tight junction, the septate junction, is localized on the basal side of the adherens junction.

Polarity proteins have distinct distributions at the AJC (Fig. 3; *the plasma membrane identity module*). The Crumbs complex is located to the apical side of the AJC (Tanentzapf and Tepass 2003), and at the primary cilium (Fan et al. 2004); the PAR complex is localized close to the AJC (Bilder et al. 2003; Izumi et al. 1998) and at the primary cilium (Sfakianos et al. 2007); and the Scribble complex is localized on the lateral membrane below the AJC (Bilder et al. 2003; Tanentzapf and Tepass 2003).

Several mechanisms regulate the different distributions of these Polarity protein complexes. In mammalian cells, the PAR complex binds through PAR3 to two cell–cell adhesion proteins, junction-associated molecule-A (JAM-A) (Ebnet et al. 2003) and nectin (Takekuni et al. 2003), that colocalize with E-cadherin in the AJC. PAR4/LKB1 also closely colocalizes with E-cadherin (Sebbagh et al. 2009), which may locally regulate its activation of PAR1 and MARKs, and thereby the organization of microtubules and the delivery of vesicles to the plasma membrane (Cohen et al. 2004a; Cohen et al. 2004b; Elbert et al. 2005).

In vitro studies indicate that binding between different PDZ domain-containing proteins in the PAR complex (PAR3 and PAR6) and Crumbs complex (PALS1 and PATJ) could be involved in positioning the Crumbs complex close to the PAR complex in the region of the AJC (Fig. 3) (Lemmers et al. 2004; Roh and Margolis 2003). Other studies in *Drosophila* have shown that restriction of Crumbs to the apical domain of epithelial cells also requires dynein-dependent basal-to-apical transport of Crumbs mRNA along microtubules and localized translation in the apical cytoplasm (Li et al. 2008). A similar mechanism may be important in apical localization of PAR3/bazooka (Harris and Peifer 2005) and Stardust (Sdt, the *Drosophila* homolog of mammalian PALS1) (Fig. 3) (Horne-Badovinac and Bilder 2008). Mechanisms involved in localization of the Scribble complex to the lateral membrane below the AJC are unknown.

Downstream Effectors of Polarity Proteins in Apical–Basal Polarity

The different distributions of Polarity protein complexes around the AJC are critical to maintaining the identity of the apical and basolateral membrane domains (Fig. 3; *plasma membrane identity module*). Genetic studies in *Drosophila* showed that the Crumbs complex is required to regulate the formation of the apical membrane, whereas the Scribble complex regulates the basolateral membrane; loss-of-function mutations in the Crumbs complex or Scribble complex result in defects in apical–basal polarity because of a loss of the apical and basolateral membrane domain, respectively (Bilder et al. 2003; Tanentzapf and Tepass 2003). Importantly, loss of either Crumbs or Scribble signaling can be compensated by decreased expression of Scribble or Crumbs, respectively, demonstrating that functions of these complexes are mutually antagonistic (Bilder et al. 2003; Tanentzapf and Tepass 2003).

Despite strong genetic evidence for the importance of these Polarity complexes in apical–basal polarity of epithelial cells, their functions remain poorly understood. This is in contrast to roles for the PAR complex, particularly aPKC, and some proteins in the Scribble complex in front–rear polarity in migrating cells (localization and activation of Rho family small GTPases, orientation of the actin and microtubule cytoskeleton, and vesicle trafficking) (see Fig. 2). Are any of these functions important for apical–basal polarity in epithelial cells?

Rho family GTPases play a number of roles in polarized epithelial cells (Fig. 3; *plasma membrane identity module*). At the adherens junction, the activities of Rac and Rho antagonize each other as Rac stabilizes junctions, whereas Rho induces actomyosin contraction

and disrupts junctions (reviewed in Wojciak-Stothard and Ridley 2002). Rac activity at junctions may be locally regulated by TIAM1, which is an aPKC substrate and Rac1 GEF (Nishimura et al. 2005); note that loss of TIAM1 results in disruption of intercellular junctions in keratinocytes (Mertens et al. 2005). Rho-induced apical constriction occurs during epithelial sheet remodeling in development. Recent studies of salivary gland invagination in the *Drosophila* embryo revealed two functions of Rho: As expected, Rho regulated actomyosin contractility through Rho-kinase (ROCK); but interestingly, Rho activity was required to maintain apical polarity of Crumbs, aPKC, and Sdt, perhaps by controlling the apical localization of Crumbs mRNA (Fig. 3) (Xu et al. 2008) (see previous discussion) (Li et al. 2008).

Several studies have identified a number of specific functions of Cdc42 in the trafficking of proteins to and from the AJC, and overall apical–basal polarity of epithelial cells. Cdc42 was initially reported to be important in stabilizing the tight and adherens junctions (Hutterer et al. 2004), and recent studies indicate that its function may be to regulate the local trafficking of proteins intrinsic to these structures through interactions with the PAR and Crumbs complexes. The Crumbs complex (Crumbs, PALS1, and PATJ) is required for the formation and maintenance of tight junctions (Fogg et al. 2005; Shin et al. 2006). A recent study in mammalian tissue culture cells showed that PALS1 and PATJ bind a Cdc42GAP called Rich1 (RhoGap-interacting with CIP4 homologs protein-1) and the scaffold protein AMOT (angiomotin) that together control Cdc42-dependent endocytosis of PALS1, PAR3, and overall tight junction permeability (Fig. 3; *endocytosis module*) (Wells et al. 2006). Significantly, a separate study in *Drosophila* reported that deletion of Cdc42, aPKC, or PAR6 resulted in discontinuities in intercellular junctions at the apex of the lateral membrane, and the formation of ectopic adherens junctions containing E-cadherin along the lateral membrane (Georgiou et al. 2008). Similar phenotypes were observed on deletion of Wasp, Arp2/3 or dynamin, indicating a requirement for actin-mediated endocytosis in the maintenance of junctional organization of E-cadherin downstream of Cdc42 (Fig. 3; *endocytosis module*) (Georgiou et al. 2008). Why might endocytosis be important in regulating the tight junction? Wells et al. suggested that regulated endocytosis would control the level of signaling activity of Polarity protein complexes (Wells et al. 2006). This is supported by the observation that defective endocytosis of Crumbs itself leads to an expanded apical domain and tumor formation, a phenotype associated with "excess" Crumbs activity (Lu and Bilder 2005).

Regulation of protein distributions at the AJC by endocytosis is balanced by directed exocytosis (Fig. 3; *the exocytosis module*). The exocyst vesicle tethering complex, which localizes to the AJC (Grindstaff et al. 1998), regulates the distribution of Polarity protein complexes. Loss-of-function mutations in the Exo84 exocyst subunit in *Drosophila* result in loss of Crumbs and the PAR complex from the AJC and their localization along the lateral membrane, and an overall decrease in the columnar morphology of cells (Blankenship et al. 2007).

The Scribble complex is localized basal to the AJC along the lateral membrane domain, but its function there is poorly understood. Perhaps Scribble, in a complex with βPIX and GIT1, locally regulates Ca^{2+}-dependent exocytosis, as it does at synapses (Fig. 3; *exocytosis module*) (Audebert et al. 2004). LGL is in a complex with the basolateral t-SNARE synataxin 4 (Musch et al. 2002). Depletion of LGL in neuronal tissue results in inhibition of some protein delivery to the plasma membrane, including N-cadherin (Klezovitch et al. 2004), but it is unknown if LGL selectively regulates delivery of basolateral proteins in epithelial cells.

Organization of the Primary Cilium

As noted earlier, the PAR complex and Crumbs-3, an isoform of the Crumbs family, are localized to the primary cilium (Fig. 3; *primary cilium module*) (Fan et al. 2004; Sfakianos et al. 2007). The primary cilium

regulates cell organization and tissue development by mechanisms that are not completely understood, and abnormal ciliogenesis is characteristic of a class of genetic diseases (ciliopathies) characterized by defects in epithelial cell polarity (e.g., polycystic kidney disease) (Singla and Reiter 2006). Deletion of Crumbs-3 inhibits ciliogenesis (Fan et al. 2004), and deletion of PAR3 or aPKC reduces the length of the cilium (Sfakianos et al. 2007). Significantly, loss of the primary cilium results in changes in intercellular junctions, defective post-Golgi delivery of apical and basolateral membrane proteins, and the partial disorganization of apical and basolateral plasma membrane domains (Overgaard et al. 2009). It is interesting to note that the centrosome, from which the basal body of the cilium is derived (Dawe et al. 2007), also plays a critical role in the global front–rear organization of migrating cells (Etienne-Manneville and Hall 2003).

Other Functions of Polarity Protein Complexes in Maintaining Apical–Basal Polarity

Although Polarity proteins have roles in controlling the structural and functional organization of apical–basal (and front–rear) polarity, it is important to recall that they are defined as tumor suppressors—deletion of one of these tumor suppressors gives rise to rapid growth, loss of the terminal differentiated state of the original cell, invasion of surrounding normal tissue, and in some cases death (De Lorenzo et al. 1999). Do these proteins have functions other than regulating the organization of cells, such as controlling cell proliferation, or is the loss of cell polarity itself causative in deregulation of cell proliferation? This question was addressed in detailed structure–function analyses of Scribble (Zeitler et al. 2004) and DLG (Hough et al. 1997) in *Drosophila*, which defined a similar domain in each protein that was required for cell polarity (LLR domain), and another (PDZ domain) that controlled cell proliferation. Although a simple conclusion is that these two functions are independent, Zeitler et al. showed that the proliferation defect induced by deletion of the PDZ domain of Scribble could be rescued by overexpression of the LRR-polarity domain (Zeitler et al. 2004). This indicates that the two functions are more likely to be linked through the role of Scribble in controlling cell polarity, i.e., loss of polarity results in deregulation of proliferation.

Studies in mammalian cells indicate, however, that the role of Scribble in the control of cell growth is even more complex (Fig. 3; *apoptosis module*). SiRNA-mediated depletion of Scribble in three-dimenional acini formed by MCF10A mammary epithelial cells had a modest effect on apical–basal polarity, but resulted in filling of the luminal space of the acini with cells (Zhan et al. 2008). This was not because of an increase in cell proliferation, but rather to a decrease in apoptosis, which is normally required to clear the luminal space of cells in this model system (Mailleux et al. 2008). SiRNA of Scribble also suppressed the increase in apoptosis normally caused by overexpression of HPV E7 or Myc, although it had no effect on E7- or Myc-induced increase in cell proliferation (Zhan et al. 2008). The effect of Scribble on apoptosis was traced back to the role of the Scribble/βPIX/GIT1 complex in activating Rac1. In addition to its effect on actin and microtubule organization, activated Rac1 induces apoptosis by activating JNK (Fig. 3; *The apoptosis module*), and in the absence of Scribble (or βPIX) this does not occur, resulting in overgrowth of cells because of lack of apoptosis (Zhan et al. 2008).

Whether other Polarity proteins play a role similar to that of Scribble in regulating cell growth is unclear. A genetic screen in *Drosophila* for mutations that enhanced tumorigenesis caused by loss of DLG expression identified a serine/threonine kinase Warts (Fig. 3; *apoptosis module*) (Zhao et al. 2008). In *Drosophila*, Warts is a downstream component of the Hippo signaling pathway that regulates organ growth. Mammalian homologs of Hippo (Mst1 and Mst2) and Warts (Lats1 and Lats2) are also tumor suppressors and loss of their expression is linked to highly aggressive

breast tumors (Reddy and Irvine 2008). Downstream targets of Warts regulate cell cycle progression (Cyclin A, B, and E) and apoptosis (the *Drosophila* homolog of baculovirus inhibitor of apoptosis 1, DIAP1) (Reddy and Irvine 2008; Zhao et al. 2008). These results indicate that DLG may also be involved in controlling cell cycle progression and apoptosis, but further studies are needed to define how it is linked to the Hippo-Warts signaling pathway. Whether other Polarity proteins are involved in regulating organ/tissue growth through proliferation or apoptosis is not known, but the effects of Scribble and DLD described previously indicate that this is likely to be an interesting area of study.

Transitions from Front–Rear to Apical–Basal Polarity

Changes in gene expression are involved in the transition from migrating cells with a front–rear polarity designed for directional migration, to an epithelium with an apical–basal polarity designed for vectorial ion and solute transport (Boyle and de Caestecker 2006; van der Flier and Clevers 2008). However, structures and cellular processes generic to both cell types are also reused or adapted, including the cytoskeleton, endocytic and exocytic vesicle trafficking pathways, and the localization of plasma membrane proteins. These remodeling events are initiated by cell–cell adhesion that instantly forms a critical membrane template for the transition from front–rear to apical–basal polarity (Fig. 4B).

The transition from front–rear polarity of migratory cells to the establishment of apical–basal polarity of simple epithelium (MET) requires the aggregation of cells (Fig. 4A) through specific cell–cell interactions, particularly those initiated by the cadherin family of Ca^{2+}-dependent adhesion proteins (Halbleib and Nelson 2006). As noted earlier, cell adhesion to the ECM is also critical for generating the formation of an apical membrane and luminal space (reviewed in Bryant and Mostov 2008). It is likely, therefore, that cell–cell adhesion, which generates "adhesive" (basolateral) and nonadhesive (apical) surfaces, and cell–ECM adhesion, which defines the axis of apical–basal polarity, combine to form the correctly oriented polarity of simple epithelial cells.

Genetic studies in mammals and *Drosophila* showed that deletion or mutations in E-cadherin resulted in disruption of the first epithelial structures, the trophectoderm of the preimplantation mouse embryo (Larue et al. 1994), and the epidermis of the *Drosophila* embryo (Wang et al. 2004). Furthermore, knockdown of E-cadherin in MDCK cells in tissue culture inhibits the establishment of cell polarity (Capaldo and Macara 2007). Other proteins are also involved in cell–cell adhesion, including members of the Ig superfamily (JAM-A and nectin).

How cells respond to cadherin-mediated cell–cell contacts to initiate the formation of functionally different plasma membrane domains is poorly understood. Initially, the establishment of cell surface polarity may be controlled at the plasma membrane by the designation of the adhesive surface/basolateral membrane formed by cell–cell contacts, and the rapid organization of microtubules and the exocytic machinery that specifies the delivery of the correct set of transport vesicles to that site (Fig. 4B). Basolateral protein accumulation at nascent cell–cell contacts in MDCK tissue culture cells requires microtubules (Shaw et al. 2007), the exocyst vesicle tethering complex, and the vesicle fusion t-SNARE syntaxin 4 (Nejsum and Nelson 2007). Microtubules may attach indirectly to the cadherin–catenin complex through interactions with the dynactin complex (Lien et al. 2008; Ligon and Holzbaur 2007), and p120catenin and kinesin 1 (Chen et al. 2003). It is also interesting to note that in migratory cells, the plus ends of microtubules are oriented to the leading edge by APC (see Fig. 2), and in polarized cells, APC is associated with microtubules at the adherens junction (Fig. 3) (Hamada and Bienz 2002). Thus, cell–cell contacts mediated by interactions between the leading edge of migrating cells would result in the localization of APC close to the forming cadherin adhesion complexes (Fig. 4).

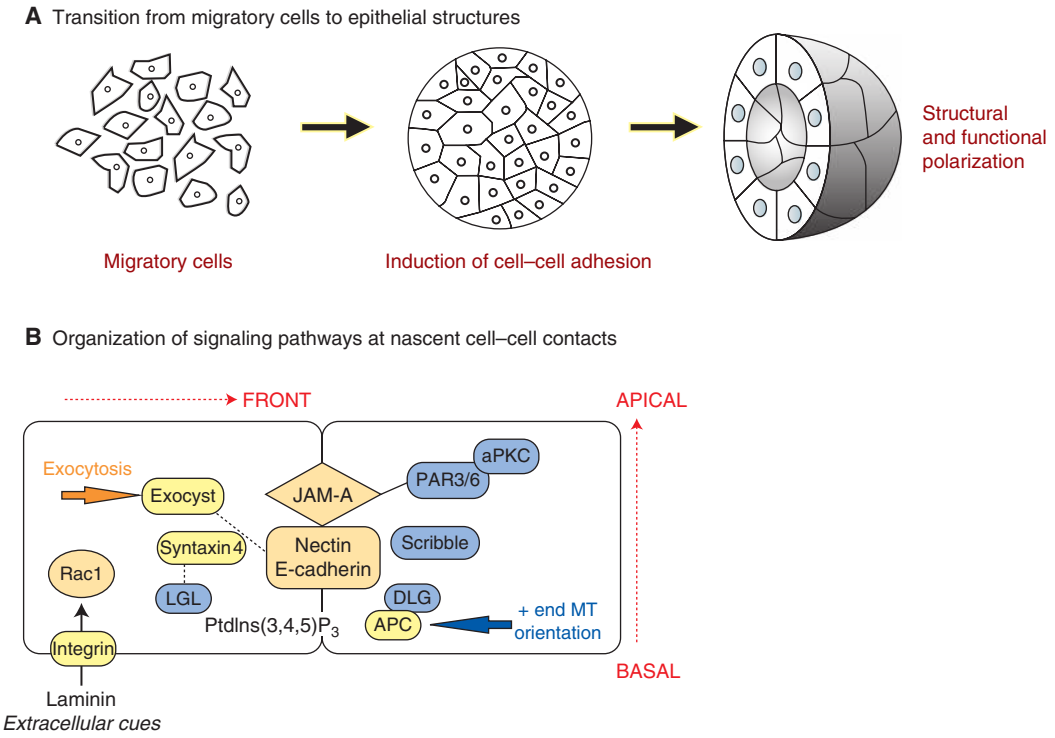

Figure 4. Transition between front–rear and apical–basal polarity. (A) Transition from migratory cells to epithelial structures. During development, migratory (mesenchymal) cells coalesce into cell aggregates through cell–cell adhesion, and following induction of the epithelial program, develop into epithelial structures (e.g., a tube). (B) Organization of signaling pathways at nascent cell–cell contacts. Migratory cells interact with each other through their leading edge (front). Cell–cell adhesion is induced by E-cadherin, and additional adhesion proteins (nectin, JAM-A). These adhesion proteins have direct (solid line) and indirect (dotted line) interactions with protein complexes important in apical–basal polarity, including the PAR complex (JAM-A) and the exocyst (directed exocytosis, E-cadherin/nectin); Scribble and LGL are also localized at the leading edge and play critical roles in regulating expocytosis through binding the t-SNARE syntaxin4. Microtubules are oriented toward the front of migrating cells through the localization of the APC (and DLG) complex at the leading edge; APC also plays a role in localizing microtubules to the AJC in the apical–basal axis in polarized epithelial cells.

Mechanisms involved in localization of the exocyst and t-SNARE to initial cell–cell contacts remain poorly understood. The exocyst is in a complex with E-cadherin and nectin, suggesting a direct recruitment of the exocyst to membrane sites of E-cadherin adhesion (Fig. 4) (Yeaman et al. 2004). Note that the exocyst is also localized to the front of migrating cells (see Fig. 2). Thus, as migrating cells recognize and contact each other, the exocyst would be in place to immediately direct transport vesicles to sites of cell–cell contacts (Fig. 4).

The PAR complex also localizes to nascent epithelial cell–cell contacts (Suzuki et al. 2002) through binding to the adhesion proteins JAM-A (Ebnet et al. 2003) and nectin (Takekuni et al. 2003). JAM-A, nectins, and the PAR complex colocalize at the AJC in fully polarized epithelial cells, where the PAR complex is critical for regulating apical–basal polarity (Fig. 3). It is possible that early recruitment of the PAR complex to initial cell–cell contacts establishes its location at the AJC between the forming apical (Crumbs complex) and

basolateral (Scribble complex) membrane domains (Fig. 4).

And Back Again—Transitions from Apical–Basal to Front–Rear Polarity

Loss of apical–basal polarity and re-initiation of front–rear polarity, termed EMT, is associated with changes in cell organization during injury (for example, see Ishibe and Cantley 2008) in response growth factors/cytokines such as hepatocyte growth factor (HGF) or transforming growth factor-β (TGF-β) and oncogenic transfomation (reviewed in Thiery and Sleeman 2006). EMT is often associated with loss of E-cadherin and other characteristics of the epithelial (apical–basal) program (Peinado et al. 2007). This change in cell polarity is a direct result of loss of expression of key components that regulate apical–basal polarity (Fig. 3; *transcription module*). HGF and TGF-β induce the expression of Snail and ZEB1, which directly repress transcription of E-cadherin (Peinado et al. 2007), the Scribble and Crumbs Polarity complexes (Aigner et al. 2007; Whiteman et al. 2008), protein trafficking pathways (De Craene et al. 2005), and ECM proteins (Spaderna et al. 2006). Reversal of EMT, following recovery from injury for example, may be controlled by down-regulation of Snail and ZEB1 by the microRNA, miR-200 (Burk et al. 2008). Interestingly, miR-200 itself is a target for ZEB1 (Burk et al. 2008), indicating a complex feedback regulation in maintaining the balance between polarity states of polarized cells (apical–basal) and migratory cells (front–rear).

CONCLUSIONS

Transitions in cellular organization from front–rear (migratory cells) to apical–basal (simple epithelia) polarity, and back to front–rear occur throughout normal development and in disease states. These transitions are signaled by soluble cues such as growth factors and receptor ligands, and changes in physical cues such as cell–ECM and cell–cell adhesion. Cellular responses to these cues involve changes in gene expression programs, and the reorganization of generic cellular machineries common to both types of cell polarity, including the cytoskeleton and vesicle trafficking pathways. Studies in a variety of cell types and organisms show that plasma membrane-associated Polarity complexes and downstream signaling pathways involving Rho family GTPases regulate the cytoskeleton and mechanisms that specify plasma membrane protein delivery, and removal and recycling by the exocytic and endocytic pathways. A major challenge is to understand how mechanisms that initiate transitions in cell polarity (e.g., from front–rear to apical–basal) are linked to mechanisms that localize and activate Polarity complexes and their downstream signaling pathways to ensure the correct remodeling of cell polarity required for a specialized function (e.g., from cell migration to vectorial ion/solute transport).

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